ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Corifollitropin alfa followed by rFSH in a GnRH antagonist protocol for poor ovarian responder patients: an observational pilot study

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Objective: To identify whether women with poor ovarian response may benefit from treatment with corifollitropin alfa in a GnRH antagonist protocol.
Design: Retrospective pilot study.
Setting: University-based tertiary care center.
Patient(s): Poor ovarian responders fulfilling the Bologna criteria developed by European Society for Human Reproduction and Embryology Consensus Group.
Intervention(s): Corifollitropin alfa (150 μg) followed by 300 IU rFSH in a GnRH antagonist protocol.
Main Outcome Measure(s): Endocrinologic profile and ongoing pregnancy rates.
Result(s): Among 43 women treated with corifollitropin alfa, mean E_2 levels showed an increasing pattern during the follicular phase, reaching 825 ng/L on the day of hCG administration, whereas FSH values showed a marked increase during the first 5 days, reaching a mean value of 35 IU/L and remaining above 20 IU/L during the late follicular phase. Cycle cancellation rate was 32.6% and embryo transfer rate 53.3%. Five patients (11.7%) had a positive hCG test and three (7%) had an ongoing pregnancy. Ongoing pregnancy rates were 11.1% per oocyte retrieval and 13% per embryo transfer. Ongoing pregnancy rates per patient did not significantly differ compared with a cohort of patients treated during 2011 with the standard protocol for poor responders in our center (short agonist-hMG) (7% vs. 6.3%).
Conclusion(s): Treatment of poor ovarian responders, as described by the Bologna criteria, with corifollitropin alfa in a GnRH antagonist protocol results in low pregnancy rates, similarly to conventional stimulation with a short agonist protocol. (Fertil Steril® 2012;■:■–■. ©2012 by American Society for Reproductive Medicine.)
Key Words: Poor responders, Bologna criteria, corifollitropin alfa, poor ovarian response, IVF

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Treatment of the poor-responder patients has been the main objective of several randomized trials over the past 20 years. More than 40 randomized trials have been published examining different treatment regimens to increase ovarian response and achieve acceptable pregnancy rates in these women (1). However, despite the flourishing literature regarding the management of these patients, none of the available treatment modalities has been universally adopted as a standard of medical care practice. Although investigators may argue that this is due to the fact that no uniform definition has been applied to this group of women, the European Society for Human Reproduction and Embryology (ESHRE) Consensus Group recently developed a new definition that might help to

Received May 10, 2012; revised September 25, 2012; accepted September 27, 2012.
N.P.P. has nothing to disclose. M.D.V. has nothing to disclose. P.H. has nothing to disclose. D.S. has nothing to disclose. C.O.-H. has nothing to disclose. P.D. has nothing to disclose. H.T. has nothing to disclose.
The Center for Reproductive Medicine receives research grants unrelated to this study from Ferring Pharmaceuticals, Merck Serono, and Merck Sharp and Dohme Corporation.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2012 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2012.09.043

describe a more uniform group of patients to be used in future clinical trials (2). However, despite this progress, the available evidence regarding treatment plans for these patients is fragmented and weak, and it is unlikely that current therapeutic options may offer a significant benefit (3). Therefore, the identification of new treatment modalities for these women appears to be crucial.

One of the most recently introduced therapeutic molecules for controlled ovarian stimulation is corifollitropin alfa, a new chimeric recombinant molecule composed of FSH and the carboxy-terminal peptide of hCG (4). This new molecule could have a potential benefit in poor ovarian responders mainly owing to its pharmacokinetic profile. Although the major advantage of corifollitropin alfa is its long elimination half-life of 68 h (5), during which it may induce and sustain multifollicular growth for an entire week (6), a key aspect of the pharmacokinetics of the molecule is the short time to reach its peak serum concentration (t_{max}). Corifollitropin alfa reaches maximum concentrations (C_{max}) 25–45 h after injection (7), a time interval that is significantly shorter compared with treatment with rFSH, in which the maximum serum concentration of rFSH is reached after 5 days of stimulation (5). Taking into account the diverse pharmacokinetic profile of corifollitropin alfa, a key question is whether this short time to peak FSH concentration could benefit the poor-ovarian-responder patient.

The rationale behind our inquiry is the fact that a rapid increase in the serum FSH concentration would result in a significantly higher exposure of the small antral follicles to constant high levels of FSH during the early follicular phase, securing not only the recruitment of the follicles, but also their continued growth. This would lead to a significantly higher number of follicles after stimulation compared with conventional gonadotrophin preparations.

Based on this theory, we decided to examine whether corifollitropin alfa may constitute a reasonable option for women with impaired ovarian response. Therefore, we retrospectively examined the files of patients with poor ovarian response treated with corifollitropin alfa in the antagonist setting to examine the efficacy of this new drug in this subgroup of patients.

METHODS

An Institutional Review Board approval was obtained for the current study (BUN 143201213488). Each of the patients had given written authorization at the time of treatment for the future use of their clinical data.

Eligibility Criteria

Eligible patients were poor ovarian responders according to the Bologna criteria (2). Eligible women should fulfill at least two of the three following criteria: 1) advanced maternal age ($\geq$40 years) or any other risk factor for poor ovarian response; 2) poor ovarian response ($\leq$3 oocytes with a conventional stimulation protocol); 3) abnormal ovarian reserve test (antral follicle count [AFC] <7 or antimüllerian hormone [AMH] <1.1 ng/mL).

Treatment Protocol

Poor ovarian responders treated with corifollitropin alfa in a GnRH antagonist protocol in our unit during the 5-month period of May to September 2011were included in the study group. Patients' files were retrospectively reviewed to examine hormonal profiles, response to stimulation, and reproductive outcome.

The stimulation consisted of a single dose of 150 μg corifollitropin alfa administered on day 2 of the treatment cycle. Five days later (day 7 of the cycle or day 5 of the stimulation), administration of a GnRH antagonist at a daily dosage of 0.25 was initiated until the day of oocyte retrieval. On day 9 of the cycle or day 7 of the stimulation, a fixed daily dose of 300 IU rFSH was administered until the day before oocyte retrieval. To induce final oocyte maturation, 10,000 IU hCG was given as soon as two or three follicles >17 mm were present on ultrasound scan. Oocytes were retrieved after 36 hours, followed by intracytoplasmic sperm injection. All embryos were transferred on day 3.

In case of monofollicular development, rescue intrauterine insemination was performed, whereas in cases with no follicular development, the treatment cycle was cancelled.

Comparative Cohort of Patients Treated with a Short GnRH Agonist Protocol

A historical group of 64 patients who fulfilled the Bologna criteria and were treated with the short GnRH agonist (GnRHa) protocol with hMG with a starting dose of 300–450 IU were selected to serve as a comparative cohort. Owing to the fact that the most common protocol for treating poor ovarian responders in our unit is the short GnRHa protocol followed by hMG, we retrospectively reviewed the files of all patients treated in 2011 with this specific protocol. Patients' files were scrutinized and women who fulfilled the Bologna criteria for poor ovarian response were considered to be eligible. All eligible patients were treated with a GnRHa initiated on day 1 of the menstrual cycle, followed by subcutaneous injections of hMG from day 2 of the cycle with a starting dose of 300–450 IU/d.

Statistical Analysis

Continuous outcomes were compared with independent *t* test or Mann-Whitney *U* test and percentages with chi-square or Fisher exact test as appropriate, with a level of significance of .05.

RESULTS

Patient Characteristics

Among 45 potentially eligible patients in the corifollitropin alfa group, two women were excluded from the final analysis: One did not fulfil the Bologna criteria and another received a lower rFSH dose after corifollitropin (200 IU instead of 300 IU).

All 64 patients in the comparative cohort group were treated with the short GnRHa protocol with hMG with a starting dose of 300–450 IU.

Patients' baseline characteristics are presented in Table 1.

TABLE 1

Baseline characteristics and outcomes in treatment and comparative cohort groups.

	Corifollitropin alfa	Short GnRH agonist
Patient characteristics		
No. of patients	43	64
Age (y), mean (SD)	37.9 (4.2)	39.1 (4.1)
BMI (kg/m^2), mean (SD)	23.6 (4.4)	25.6 (6.0)
Stimulation characteristics, mean (SD)		
Stimulation days	9.6 (2.3)	9.0 (2.9)
Days of additional rFSH	3.78 (2.4)	NA
Stimulation units of rFSH	1,133 (722)	NA
Ovarian response		
Cycles with oocyte retrieval, n (%)	27 (62.8)	45 (70)
Mean no. of oocytes,* mean (SD)	3.48 (1.2)	3.37 (2.3)
Cycles cancelled, n (%)	14 (32.6)	18 (28.1)
Cycles with embryo transfer, n (%)	23 (53.5)	34 (53.1)
Reproductive outcome, %		
Positive hCG/started cycle	11.7	10.9
Positive hCG/OPU	18.5	15.6
Positive hCG/ET	21.7	20.6
Ongoing pregnancy/started cycle	7	6.3
Ongoing pregnancy/OPU	11.1	9
Ongoing pregnancy/ET	13	12

Note: BMI = body mass index; ET = embryo transfer; OPU = oocyte pickup; NA = nonapplicable.
* Mean number refers only to patients with oocyte retrieval.

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Treatment with Corifollitropin Alfa

Endocrine profile. The hormonal profile during the ovarian stimulation period is described in Figure 1. As shown, it appears that the mean E_2 levels followed an increasing pattern during the follicular phase until the day of oocyte retrieval, with a mean E_2 value of 825 ng/L on the day of hCG administration.

FSH values showed a marked increase during the first 5 days of stimulation (cycle day 7), reaching a mean value of 35 IU/L on the day of GnRH antagonist administration. Despite a small drop of FSH levels on day 7 of stimulation (day of initiation of rFSH), to a mean value of 23 IU/L, the serum FSH levels remained above 20 IU during the late follicular phase and until ovulation triggering.

Ovarian response and embryo transfer. Data regarding responses to stimulation are presented in Table 1. Fourteen patients (32.6%) had a cycle cancellation due to either lack of follicular development or monofollicular recruitment. At least one oocyte was retrieved in 27 patients (62.8%), yielding a mean (SD) of 3.48 (1.2) oocytes retrieved. The mean (SD) number of stimulation days was 9.6 (2.3) in the whole population and 10.4 (2.2) in patients having at least one oocyte retrieved during oocyte pick-up (OPU). The mean number of stimulation days was 10.78 (2.4). The majority of the patients reaching oocyte retrieval needed additional rFSH, with 24 patients (89%) needing at least one additional day of rFSH. The mean number of days of additional rFSH was 3.78 (2.4), and the mean additional rFSH dose after administration of corifollitropin alfa was 1,133 (722) IU.

Twenty-three patients had at least one embryo available for transfer, leading to a cumulative transfer rate of 53.5% and a mean number of embryos transferred of 1.74 (0.81). Four patients (9.3%) had one or more embryos cryopreserved.

Reproductive outcome. As shown in Table 1, five patients had a positive serum hCG 14 days after ET, yielding a positive hCG rate of 11.7% per started cycle, 18.5% per oocyte retrieval and 21.7% per embryo transfer. Two patients had a biochemical pregnancy resulting in an ongoing pregnancy rate of 7% per started cycle, 11.1% per oocyte retrieval and 13% per embryo transfer.

Pregnancies occurred in patients both $<$40 years old (2/23) and $\geq$40 years old (1/20). All of the three women that had an ongoing pregnancy after treatment with corifollitropin alfa had a previous treatment cycle with fewer than four oocytes retrieved and an AMH value of $<$1.1 ng/L, whereas two out of three had an AFC of $<$7.

No multiple pregnancies occurred, and none of the patients reported any adverse effect linked to treatment with corifollitropin alfa.

Comparison with the Cohort Treated with a Short GnRHa Protocol

Comparison of the outcomes in the study group with the cohort of patients treated with a short GnRHa protocol shows that outcomes were similar in both groups (Table 1).

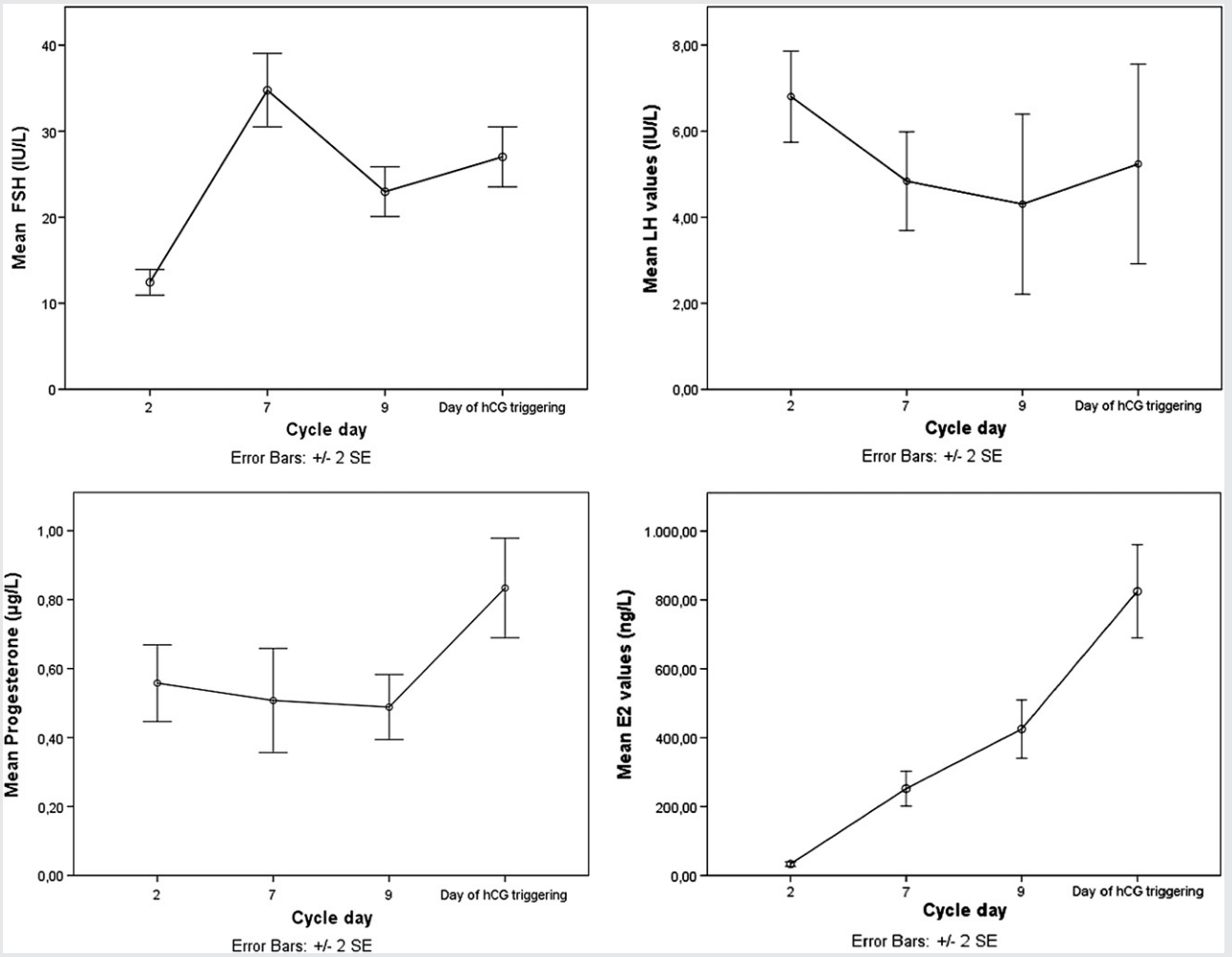
Cancellation rates in the control group were similar to those of the corifollitropin alfa group (70% vs. 63%; P=.42), and no significant difference was observed in oocyte retrieval rates (28% vs. 33%; P=.62) or embryo transfer rates (53% vs. 54%; P=.97). Finally, ongoing pregnancy rates per patient were consistently low in both groups, with only four pregnancies among the 64 women (6.3%) in the control group and three among the 43 women (7%) in the corifolitropin alpha group (P=.74).

DISCUSSION

This study is the first to examine the effect of corifollitropin alfa in poor-ovarian-responder patients selected according to the Bologna criteria. According to our results it appears that, although corifollitropin alfa induces a hormonal response that may be considered satisfactory, the number of cancelled cycles remains high and the cumulative transfer and ongoing pregnancy rates are low in this group of patients.

Despite the fact that pregnancy rates observed in this cohort of patients were low, it appears that corifollitropin alfa successfully augmented E_2 levels and resulted in an acute rise of serum FSH levels, as initially hypothesized. This low pregnancy rate, despite the sharp increase in serum FSH levels achieved following treatment with corifollitropin alfa, should definitely raise concerns regarding the anticipated ovarian response and the reproductive potential of "Bologna poor responders." Although earlier studies claimed a benefit of other stimulation protocols in women with poor ovarian response (8, 9), none of those studies adopted the latest ESHRE definition for poor ovarian responders (2) as an inclusion criterion. Therefore, it is still unclear whether the low ongoing pregnancy rate in the present study should be

FIGURE 1



Endocrinologic profiles during the follicular phase of patients treated with corifollitropin alfa.

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interpreted as a negative outcome or as a satisfactory outcome in this very poor prognosis population.

Corifollitropin alfa has been shown to be highly effective in normal ovarian responders, with the number of oocytes retrieved being significantly higher compared with rFSH and with similar pregnancy rates (10). The crucial question, however, is how poor the prognosis is for patients selected according to this new ESHRE definition. Data from our center show that among poor ovarian responders who fulfill the Bologna criteria, natural-cycle IVF may result in a cumulative ongoing pregnancy rate per patient of 7.4% after five consecutive cycles (11). Taking this into account, it appears that one cycle with corifollitropin alfa results in an ongoing pregnancy rate similar to that of five consecutive natural IVF cycles. This outcome can by no means be considered disappointing, but on the contrary is rather promising in view of the extremely poor prognosis of this patient subgroup. However, compared with a historical control group of "Bologna poor responders" treated with a short GnRHa protocol, it appears that corifollitropin alfa, in the current protocol, did not at all increase pregnancy rates.

A major strength of the present study is that it is the first trial to include a group of consecutive patients who were poor responders according to the recently developed Bologna criteria (2). Furthermore, it is the first study to examine the effect of corifollitropin alfa in women exhibiting poor ovarian response. However, one has to acknowledge that the present study was an observational pilot study, aiming to identify the level of response among these patients and to provide insight into the actual potential of this new treatment modality for poor ovarian responders. In addition, although a historical group of women treated with a short GnRHa protocol was selected as a comparative cohort, the lack of randomization and the retrospective design of the study prevent us from drawing firm conclusions regarding the effect of corifollitropin alfa compared with other stimulation protocols in poor ovarian responders as described by the new ESHRE definition.

Future implications derived from our study should focus on two different directions. First, one should consider that although corifollitropin alfa performed modestly in poor ovarian responders when administered in a GnRH antagonist setting, hypothetically a better performance might be found in a GnRHa setting. Earlier randomized trials in poor ovarian responder patients have shown that the long GnRHa protocol results in a significantly higher response and higher pregnancy rates compared with the GnRH antagonist protocol (12), whereas in normal responders, corifollitropin alfa in a GnRHa protocol resulted in a higher number of oocytes retrieved (13). Therefore, it would be of interest to examine the effect of corifollitropin alfa in a long GnRHa protocol in women with poor ovarian response.

In addition, in the present trial, the stimulation after cycle day 9 was performed with 300 IU rFSH. Although rFSH versus hMG did not show any difference in the GnRH antagonist setting (14), a previous report has shown that the addition of hMG to FSH may improve embryo quality and result in an increase in pregnancy rates (15). Consequently, future trials need to examine whether cotreatment with hMG from day 9 after treatment with corifollitropin alfa in a GnRH antagonist cycle results in a higher pregnancy rate.

A second direction for future research is the evaluation of the reproductive potential of Bologna criteria patients. The Bologna criteria, though appearing to be operational, may refer to women having a very limited benefit of ovarian stimulation. The present study and an earlier study from our group (11) highlight the fact that the pregnancy rates among Bologna poor responders are very low with either intense stimulation or natural-cycle IVF. Consequently, given that currently no prospective trial has enrolled poor ovarian responders based on the new criteria, future trials testing other treatment modalities in these women should be performed. This may further clarify whether the Bologna criteria actually refer to patients who would benefit from oocyte donation rather than controlled ovarian stimulation.

In conclusion, the present study represents the first to assess the effect of corifollitropin alfa in poor ovarian responders and the first study examining the effect of an ovarian stimulation protocol in poor responders as described by the Bologna criteria. Corifollitropin alfa in a GnRH antagonist setting does not appear to significantly increase pregnancy rates; however, pregnancy rates in this subgroup of women are also low after treatment with a short GnRHa protocol. Future trials are needed to determine the reproductive potential of the "Bologna-criteria poor ovarian responders" and to investigate the effect of corifollitropin alfa in a GnRHa setting.

Acknowledgments: The authors thank Walter Meul for his invaluable help during data collection and abstraction.

REFERENCES

1. Polyzos NP, Devroey P. A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel? Fertil Steril 2011;96:1058–61.e7.
2. Ferraretti AP, la Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. ESHRE consensus on the definition of "poor response" to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod 2011;26:1616–24.
3. Frydman R. Poor responders: still a problem. Fertil Steril 2011;96:1057.
4. Fares FA, Suganuma N, Nishimori K, LaPolt PS, Hsueh AJ, Boime I. Design of a long-acting follitropin agonist by fusing the C-terminal sequence of the chorionic gonadotropin beta subunit to the follitropin beta subunit. Proc Natl Acad Sci U S A 1992;89:4304–8.
5. Fauser BC, Alper MM, Ledger W, Schoolcraft WB, Zandvliet A, Mannaerts BM. Pharmacokinetics and follicular dynamics of corifollitropin alfa versus recombinant FSH during ovarian stimulation for IVF. Reprod Biomed Online 2010;21:593–601.
6. Fauser BC, Mannaerts BM, Devroey P, Leader A, Boime I, Baird DT. Advances in recombinant DNA technology: corifollitropin alfa, a hybrid molecule with sustained follicle-stimulating activity and reduced injection frequency. Hum Reprod Update 2009;15:309–21.
7. Devroey P, Fauser BC, Platteau P, Beckers NG, Dhont M, Mannaerts BM. Induction of multiple follicular development by a single dose of long-acting recombinant follicle-Stimulating hormone (FSH-CTP, corifollitropin alfa) for controlled ovarian stimulation before in vitro fertilization. J Clin Endocrinol Metab 2004;89:2062–70.
8. Fabregues F, Penarrubia J, Creus M, Manau D, Casals G, Carmona F, et al. Transdermal testosterone may improve ovarian response to gonadotrophins in low-responder IVF patients: a randomized, clinical trial. Hum Reprod 2009;24:349–59.
9. Demirol A, Gurgan T. Comparison of microdose flare-up and antagonist multiple-dose protocols for poor-responder patients: a randomized study. Fertil Steril 2009;92:481–5.
10. Devroey P, Boostanfar R, Koper NP, Mannaerts BM, Ijzerman-Boon PC, Fauser BC. A double-blind, noninferiority RCT comparing corifollitropin alfa and recombinant FSH during the first seven days of ovarian stimulation using a GnRH antagonist protocol. Hum Reprod 2009;24:3063–72.
11. Polyzos NP, Blockeel C, Verpoest W, de Vos M, Stoop D, Vloeberghs V, et al. Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria. Hum Reprod 2012 August 30, 2012. [Epub ahead of print.]
12. Malmusi S, la Marca A, Giulini S, Xella S, Tagliasacchi D, Marsella T, et al. Comparison of a gonadotropin-releasing hormone (GnRH) antagonist and GnRH agonist flare-up regimen in poor responders undergoing ovarian stimulation. Fertil Steril 2005;84:402–6.
13. Fatemi HM, Oberye J, Popovic-Todorovic B, Witjes H, Mannaerts B, Devroey P. Corifollitropin alfa in a long GnRH agonist protocol: proof of concept trial. Fertil Steril 2010;94:1922–4.
14. Devroey P, Pellicer A, Nyboe Andersen A, Arce JC. A randomized assessor-blind trial comparing highly purified hMG and recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer. Fertil Steril 2012;97:561–71.
15. Requena A, Landeras JL, Martinez-Navarro L, Calatayud C, Sanchez F, Maldonado V, et al. Could the addition of hp-hMG and GnRH antagonists modulate the response in IVF-ICSI cycles? Hum Fertil (Camb) 2010;13:41–9.

1 **Corifollitropin alfa followed by rFSH in a GnRH antagonist protocol for poor ovarian responder patients: an observational pilot study**

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Although pregnancy rates in "Bologna-criteria poor ovarian responders" treated with corifollitropin alpha in a GnRH antagonist protocol are low, this should be interpreted with caution, given the very poor prognosis of this population.